UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte HARRY R. DAVIS

Appeal No. 2006-3204
Application No. 10/057,629

ON BRIEF

Before GRIMES, GREEN, and LEBOVITZ, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1, 8-11, 13-24, 32-45 and 53-56.[1] Claim 1 is representative of the claims on appeal, and reads as follows:

> 1. A method of treating sitosterolemia, comprising administering to a mammal in need of such treatment an effective amount of at least one sterol absorption inhibitor, or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or prodrug of the at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate of the least one sterol absorption inhibitor, or mixture thereof.

[1] Claims 2-7, 12, 25-31, 46, 57 and 58 are also pending, but stand withdrawn from consideration as being drawn to a non-elected invention. See Appeal Brief, page 1. In addition, appellant elected the species of ezetimibe as the sterol adsorption inhibitor, cholestyramine as the lipid lowering agent, and simvastatin as the third therapeutic agent. See id. at 4-5

Claims 1, 8, 9, 10, 11, 13-24, 32-45 and 53-56 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Rosenblum[2] and Belamarich.[3] After careful review of the record and consideration of the issues before us, we reverse.

BACKGROUND

According to the specification:

> Sitosterolemia is a genetic lipid storage disorder characterized by increased levels of sitosterol and other plant sterols in the plasma and other tissues due to increased non-selective intestinal absorption of sterols and decreased hepatic removal. Individuals having sitosterolemia can exhibit one or more of the following conditions: tendon and tuberous xanthomas, arthritis, hemolytic episodes, accelerated atherosclerosis and myocardial infarctions, and can die at an early age due to extensive coronary atherosclerosis.

Id. at 1.

DISCUSSION

Claims 1, 8, 9, 10, 11, 13-24, 32-45 and 53-56 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Rosenblum and Belamarich.

Rosenblum is cited for teaching the use of ezetimibe, a sterol adsorption inhibitor, with an HMG-CoA reductase inhibitor, such as simvastatin, in lowering cholesterol and reducing the risk of atherosclerosis. See Examiner's Answer, page 3. The examiner acknowledges that Rosenblum "does not expressly teach

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[2] Rosenblum et al. (Rosenblum), U.S. Patent No. 5,846,966, issued December 8, 1998.
[3] Belamarich et al. (Belamarich), "Response to Diet and Cholestyramine in a Patient with Sitosterolemia," Pediatrics, Vol. 86, No. 6, pp. 977-81 (1990).

. . . employing . . . ezetimibe with simvastatin, a HMG-CoA reductase inhibitor and/or cholestyramine, . . . to treat sitosterolemia." Id. at 4.

Belamarich is cited for teaching that "hypercholesterolemia is one of the manifestation[s, sic] of sitosterolemia," and that a low-sterol diet, as well as cholestyramine, are effective in lowering sterol and cholesterol levels in sitosterolemic patients. Id.

The examiner concludes:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ ezetimibe with simvastatin and/or cholestyramine, . . . to treat sitosterolemia.
>
> One of ordinary skill in the art would have been motivated to employ ezetimibe with simvastatin and/or cholestyramine, . . . to treat sitosterolemia. [Rosenblum] teaches the combination of simvastatin and ezetimibe as useful in reducing cholesterol level. Employing the combination of simvastatin and ezetimibe in a method to reduce cholesterol level and thereby treating sitosterolemia, a condition known to have elevated cholesterol level, would have been reasonably expected to be effective, absent evidence to the contrary. Moreover, cholestyramine is known to be effective in lowering cholesterol in sitosterolemic patient. Therefore, administering all three compounds concomitantly for the very same purpose would have been obvious to one of ordinary skill in the art (See *In re Kerkhoven*, 205 USPQ 1069).

Id. at 4-5.

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) (citations omitted). The test of obviousness is "whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention."

In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). Appellant argues that the examiner has failed to establish a prima facie case of obviousness. See Appeal Brief, page 10. We agree, and the rejection is reversed.

As noted by appellant, Rosenblum, while teaching that ezetimibe, optionally in combination with an HMG-CoA reductase inhibitor such as simvastatin, may be used for reducing the cholesterol and the risk of atherosclerosis, does not teach or suggest the use ezetimibe in the treatment of sitosterolemia. See id. at 11.

Belamarich teaches that patients with sitosterolemia "are frequently hypercholesterolemic with elevated levels of low-density lipoprotein (LDL) cholesterol." Belamarich, page 977, second column. While Belamarich teaches that sitosterolemia may be treated with cholestyramine, a bile sequestering resin, it does not teach or suggest the use of ezetimibe.

The examiner's rationale for the combination appears to be that since patients with sitosterolemia are frequently hypercholesterolemic, and Rosenblum teaches that ezetimibe optionally in combination with an HMG-CoA reductase inhibitor is used to lower cholesterol, it would have been obvious to the ordinary artisan to use ezetimibe optionally in combination with an HMG-CoA reductase inhibitor to treat sitosterolemia.

We find that the examiner's reasoning to be flawed, however, as the art established that compounds that are used to treat hypercholesterolemia may not be useful in the treatment of sitosterolemia. See Appeal Brief, pages 12-14.

Appellant cites Hidaka,[4] Nguyen[5] and Salen,[6] all of which teach that HMG-CoA reductase inhibitors such as lovastatin and pravastatin are ineffective in the treatment of sitosterolemia.

Thus, Hidaka teaches that "[p]ravastatin had little effect in a sitosterolemic patient on plasma levels of sterols, where cholestyramine decreased the plasma levels of both cholesterol and cholestanol." Hidaka, abstract. Salen teaches that "[l]ovastatin, a competitive inhibitor of cholesterol biosynthesis that is widely used in the treatment of hypercholesterolemia has been tried but has not been an effective treatment in sitosterolemia." Salen, page 952, paragraph bridging the two columns. Nguyen also teaches that lovastatin is "ineffective" in the treatment in sitosterolemia. Nguyen, page 1942, first column. Moreover, Nguyen suggests that differences in responses may be used diagnostically. Specifically, Nguyen teaches that "[t]he therapies with cholestyramine and lovastatin not only support our contention of the fundamental abnormality in the regulation of cholesterol biosynthesis that underlies sitosterolemia, but the response to these therapies can also be used to detect sitosterolemia. . . . Therefore, the failure to respond to lovastatin and a substantial response to cholestyramine may suggest sitosterolemia . . . ." Id. at page 1946, second column.

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[4] Hidaka et al. (Hidaka), "Effects of an HMG-CoA Reductase Inhibitor, Prevastatin, and Bile Sequestering Resin, Cholestyramine, on Plasma Plant Sterol Levels in Hypercholesterolemic Subjects," Journal of Atherosclerosis and Thrombosis, Vol. 2, No. 1, pp. 60-65 (1995).

[5] Nguyen et al. (Nguyen), "Regulation of cholesterol biosynthesis in sitosterolemia: effects of lovastatin, cholestyramine, and dietary sterol restriction," Journal of Lipid Research, Vol. 32, pp. 1941-48 (1991).

[6] Salen et al. (Salen), "Sitosterolemia," Journal of Lipid Research, Vol. 33, pp. 945-55 (1992).

Therefore, the references as combined do not teach or suggest that known cholesterol lowering agents may be used in the treatment of sitosterolemia, but in fact teach that patients with sitosterolemia respond differently to known cholesterol-lowering agents than hypercholesterolemic patients, and we find that the examiner has not set forth a prima facie case of obviousness. Moreover, even if we were to assume for the sake of argument that the combination suggests the use of ezetimibe in the treatment of sitosterolemia, at most, it merely would have obvious to try its use, "[b]ut, 'obvious to try' is not the standard," and the rejection of the claims must be reversed. Ecolochem, Inc. v. Southern California Edison Co., 227 F.3d 1361, 1374, 56 USPQ2d 1065, 1075 (Fed. Cir. 2000).

The dissent bases its conclusion that it would have been obvious to use ezetimibe to treat sitosterolemia "[b]ased on the similar mechanisms of action of cholestyramine and ezetimibe."

Rosenblum, however, discloses that ezetimibe exerts its therapeutic effect "by virtue of [its] ability to inhibit absorption and/or esterification of cholesterol." Rosenblum, col. 20, lines 44-46. In contrast, cholestyramine is a bile-sequestering resin. See Hikada, abstract. That is, cholestyramine is a quaternary ammonium exchange resin with a polystyrene polymer skeleton, and, as the chloride salt, it binds to bile acids. See Casdorph,[7] page 293, column 1. With the increased loss of bile acids in stool, there is also a reduction in serum

[7] Casdorph, "Hypercholesteremia: Treatment with Cholestyramine, a Bile Sequestering Resin," California Medicine, Vol. 106, pp. 293-95 (1967).

cholesterol. Id. Therefore, the only similarity that ezetimibe and cholestyramine is that both have been shown to lower cholesterol in hypocholestermic patients. But, by the dissent's reasoning, all classes of cholesterol lowering drugs would have "similar mechanisms of action."

As indicated by the evidence submitted by appellants, not all cholesterol lowering agents are effective in treating sitosterolemia. The physiological defect in sitosterolemia is the increase in intestinal absorption of dietary plant sterols, not the metabolism of cholesterol. The assumption that all cholesterol lowering agents would be effective in the treatment of sitosterolemia was demonstrated to be incorrect as statins were shown to be ineffective in treating sitosterolemia. Thus, once the assumption was proven wrong, there would have been no expectation of using other cholesterol lowering agents in the treatment of sitosterolemia.

CONCLUSION

Because the examiner has failed to set forth a prima facie case of obviousness, the rejection over the combination of Rosenblum and Belamarich is reversed.

REVERSED

Lora M. Green
Administrative Patent Judge

Richard M. Lebovitz
Administrative Patent Judge

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GRIMES, Administrative Patent Judge, dissenting in part.

I agree that the cited references would not have led those skilled in the art to administer an HMG-CoA reductase inhibitor to patients having sitosterolemia. In my opinion, however, the evidence of record would have suggested using ezetimibe to treat sitosterolemia to those skilled in the art. I would reverse the rejection of the claims that require administering an HMG-CoA reductase inhibitor but affirm the rejection of the remaining claims.

The claims are directed to a method of treating sitosterolemia by administering a sterol absorption inhibitor, ezetimibe being the elected species. The examiner rejected the claims as obvious in view of Rosenblum and Belamarich. Belamarich discloses that

> [t]he metabolic defect [underlying sitosterolemia] is related to a five-fold or greater increase in intestinal absorption of dietary plant sterols compared with subjects who do not have sitosterolemia. Failure to excrete plant sterols in the bile has also been implicated as a contributing factor.

Page 977, right-hand column. Belamarich also teaches that

> [p]atients with sitosterolemia are frequently hypercholesterolemic . . . , however, the hypercholesterolemia of sitosterolemia is responsive to cholesterol-lowering diets, bile acid binding resins, and ileal bypass surgery.

Id.

Belamarich reports that treating a patient with a combination of a low-sterol diet and cholestyramine, a bile acid binding resin, "evoked a 40% decrease in plasma cholesterol and a 42% reduction of plasma sitosterol concentration. These findings confirm previous observations of the effectiveness of cholestyramine in sitosterolemia." Page 980, left-hand column.

Salen, cited by Appellant (Appeal Brief, page 14), shows how Belamarich would have been understood by those of skill in the art. Salen teaches that cholestyramine produces "bile acid malabsorption." Page 951, left-hand column. That is, cholestyramine interferes with absorption of sterol-containing bile acids in the digestive tract, with the result that the bile acids and their component sterols are excreted in the stool and eliminated from the patient's body.

Rosenblum teaches that "[w]hen intestinal cholesterol absorption is reduced, by whatever means, less cholesterol is delivered to the liver. . . . Thus, the net effect of inhibiting intestinal cholesterol absorption is a decrease in plasma cholesterol levels." Column 2, lines 6-12. Rosenblum also teaches that "[c]ombination therapy of an HMG CoA reductase inhibitor and a bile acid sequestrant [a.k.a. bile acid binding resin] has been demonstrated to be more effective in human hyperlipidemic patients than either agent in monotherapy." Column 2, lines 17-21.

Rosenblum teaches that compounds like ezetimibe "have been found to inhibit the intestinal absorption of cholesterol and to significantly reduce the formation of liver cholesteryl esters in animal models." Column 20, lines 41-44.[8] Rosenblum teaches that ezetimibe can be administered to reduce serum cholesterol levels either alone (column 3, lines 44-49) or in combination with a "cholesterol biosynthesis inhibitor" (column 3, lines 54-67) such as an HMG-CoA reductase inhibitor (column 6, lines 37-40)

[8] Appellant does not dispute that Rosenblum's genus encompasses ezetimibe. See the Appeal Brief, page 11 ("Rosenblum et al. disclose that ezetimibe, optionally in combination with an HMB-CoA reductase inhibitor . . . , is useful for reducing cholesterol.").

I agree with the examiner that these teachings would have made it obvious to administer the ezetimibe taught by Rosenblum to a patient having sitosterolemia. Motivation to do so is provided by the cited references: Belamarich teaches that cholestyramine, a bile-acid binding resin, is an effective treatment for sitosterolemia. Those skilled in the art recognized that bile acid binding resins act by inhibiting absorption of sterol-containing bile acids. See Salen. Rosenblum teaches that ezetimibe inhibits intestinal absorption of cholesterol. Based on the similar mechanisms of action of cholestyramine and ezetimibe, and the known effectiveness of cholestyramine in treating sitosterolemia, those of skill in the art would have been led to administer ezetimibe with a reasonable expectation that it would be an effective treatment of sitosterolemia.

The majority focuses on the reasoning that the examiner provided for combining the references: that it would have been obvious to use a combination of simvastatin, ezetimibe, and cholestyramine to treat patients having sitosterolemia because those patients also suffer from high serum cholesterol (hypercholesterolemia) and Rosenblum teaches that the combination of simvastatin and ezetimibe is effective in lowering serum cholesterol. The majority finds this reasoning flawed because the evidence of record shows that HMG-CoA reductase inhibitors (i.e., statins such as simvastatin) are ineffective in lowering cholesterol levels in sitosterolemic patients.

I agree with my colleagues that the prior art of record would not have led those skilled in the art to expect a statin to lower cholesterol levels in a patient

with sitosterolemia. Therefore, I agree that the rejection of claims 16-18, 22-24, 33, 41, 42 should be reversed.

The remaining claims, however, do not require administering a statin. Statins act in a completely different way than cholestyramine and ezetimibe. Statins inhibit cholesterol biosynthesis (Rosenblum; column 6, lines 37-39), while cholestyramine and ezetimibe inhibit sterol absorption. The defect underlying sitosterolemia was known to involve sterol absorption (Belamarich; page 977, right-hand column). Therefore, the ineffectiveness of statins would not, in my opinion, have led those skilled in the art to doubt the effectiveness of treating sitosterolemia with ezetimibe. For the reasons discussed above, I conclude that claims 1, 8-11, 13-15, 19-21, 32, 34-40, 43-45 and 53-56 would have been obvious to those of ordinary skill in the art. I would affirm the rejection of those claims.

Appellant argues that the references would not have suggested that ezetimibe would be useful for treating sitosterolemia. Appeal Brief, pages 11-13. This argument is adequately addressed above. In addition, Appellant argues that the claimed method solved a long-felt need in the art. Appellant cites Hidaka and Nguyen as evidence that "those of ordinary skill in the art were working on the problem of treating sitosterolemia without the deleterious side effects associated with cholestyramine." Id., page 14. Appellant cites Steiner as evidence that "this long-felt need has been successfully satisfied by Zetia® ezetimibe formulation." Id., page 16. Appellant concludes that the claimed method "has successfully met" the "need for a treatment for sitosterolemia with

less likelihood of deleterious side effects such as those associated with treatment with cholestyramine." Id., page 18.

The majority reverses for lack of a prima facie case and thus has no need to address this argument. I would reach it, but I find it unpersuasive for the following reasons. First, although Hidaka states that cholestyramine can have side effects,[9] it does not disclose a specific problem and provide evidence that those in the art were attempting to solve that problem. "[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem." Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1178, 26 USPQ2d 1018, 1029 (Fed. Cir. 1993). Neither Hidaka nor any other reference identified by Appellant articulates a specific, identified problem with existing sitosterolemia treatments and provides evidence of efforts to solve that problem.

Second, Appellant defines the need allegedly met by ezetimibe as a "need for a treatment for sitosterolemia with less likelihood of deleterious side effects such as those associated with treatment with cholestyramine." Appeal Brief, page 18. This definition of the "long-felt need", in addition to lacking support in the evidence, sets the bar too low to be useful in an obviousness analysis. Under Appellant's standard, any incremental improvement in a method of treatment would satisfy a "long-felt need" if it is more effective, or effective in more patients, than pre-existing treatments. Thus, for example, substituting

[9] "The patient had been treated with cholestyramine, but unfortunately could not tolerate the treatment because of her associated hemorrhoids." Page 61, right-hand column.

ibuprofen for aspirin or acetaminophen, in a formulation containing pseudoephedrine, would be considered nonobvious if the new composition did the same thing as the old ones but had fewer side-effects. This is not the appropriate standard. Cf. Richardson-Vicks, Inc. v. Upjohn Co., 122 F.3d 1476, 1483-84, 44 USPQ2d 1181, 1187 (Fed. Cir. 1997).

Finally, whether an invention satisfied a long-felt need, and what relevance that has to obviousness, must be considered in light of the state of the art at the time the invention was made: that an invention satisfied a long-felt need has little relevance to obviousness if the means for satisfying that need became available in the art only recently. See, e.g., Graham vs. John Deere Co., 383 U.S. 1, 36, 148 USPQ 459, 474 (1966) ("At the latest, those differences [between the claimed and prior art products] were rendered apparent in 1953 by the appearance of the Livingstone patent, and unsuccessful attempts to reach a solution to the problems confronting [the inventor] made before that time became wholly irrelevant."); In re Sabatino, 387 F.2d 981, 986, 156 USPQ 212, 216 (CCPA 1968) ("[T]he evidentiary value of the many apparently unsuccessful attempts to [solve the problem addressed by the invention] appears to be well-tempered by the fact that those attempts occurred before Rigsby, the most pertinent reference, became available to those in the art.").

Therefore, any need that existed before ezetimibe was known to those skilled in the art is irrelevant to the question at hand – whether it would have been obvious to use ezetimibe to treat sitosterolemia.

Here, the evidence appears to show that ezetimibe became known to those skilled in the art as of December 8, 1998 (the issue date of Rosenblum). The instant application claims an effective filing date of January 6, 2001. Therefore, it appears that there was a time period of only two years and one month between the time ezetimibe became known in the art and the time Appellant filed an application claiming its use to treat sitosterolemia.

Appellant's position – that the evidence shows nonobviousness because there was a long-felt need for alternative sitosterolemia treatments and no one else thought to use ezetimibe before he did – is undercut by the short time period between the time ezetimibe became known to those skilled in the art and the time Appellant filed his application. In sum, Appellant's evidence of long-felt need is at best weak evidence of nonobviousness and does not overcome the prima facie case.

Eric Grimes
Administrative Patent Judge

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